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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-023

Allergan, Inc.
Attention: Elizabeth Bancroft
Senior Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623-9534

Dear Ms. Bancroft:

Please refer to your new drug application (NDA) dated February 24, 1999, received February 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Restasis (cyclosporine ophthalmic emulsion) Ophthalmic Emulsion, 0.05%.

We acknowledge receipt of your submissions dated September 7, 2001, and April 23, May 22, June 17, July 11, September 6, October 28, November 15, and December 4, 6, 16 and 20, 2002.

We also refer to our approvable letters of August 3, 1999, and March 25, and October 19, 2000. The September 6, 2002, submission constituted a complete response to our October 19, 2000, action letter.

This new drug application provides for the use of Restasis (cyclosporine ophthalmic emulsion) Ophthalmic Emulsion, 0.05% for the following indication: to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed labeling text

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert, immediate container and carton labels. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-023.**" Approval of this submission by FDA is not required before the labeling is used.

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In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

(See appended electronic signature page)

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

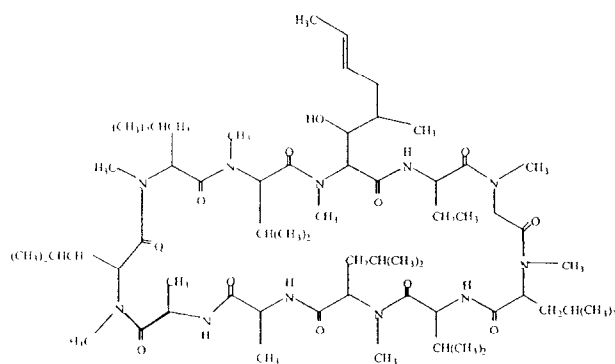
RESTASIS™

(cyclosporine ophthalmic emulsion) 0.05%

Sterile, Preservative-Free

DESCRIPTION

RESTASIS™ (cyclosporine ophthalmic emulsion) 0.05% contains a topical immunomodulator with anti-inflammatory effects. Cyclosporine's chemical name is Cyclo[[*(E)*-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl] and it has the following structure:

Formula: C₆₂H₁₁₁N₁₁O₁₂

Mol. Wt. 1202.6

Cyclosporine is a fine white powder. RESTASIS™ appears as a white opaque to slightly translucent homogeneous emulsion. It has an osmolality of 230 to 320 mOsmol/kg and a pH of 6.5 to 8.0.

Each mL of RESTASIS™ contains: **Active:** cyclosporine 0.05%. **Inactives:** glycerin, castor oil, polysorbate 80, carbomer 1342, purified water, and sodium hydroxide to adjust the pH.

CLINICAL PHARMACOLOGY**Mechanism of action:**

Cyclosporine is an immunosuppressive agent when administered systemically.

In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, cyclosporine emulsion is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

Pharmacokinetics:

Blood cyclosporine A concentrations were measured using a specific high pressure liquid chromatography-mass spectrometry assay. Blood concentrations of cyclosporine, in all the samples collected, after topical administration of RESTASIS™ 0.05%, BID, in humans for up to 12 months,

were below the quantitation limit of 0.1 ng/mL. There was no detectable drug accumulation in blood during 12 months of treatment with RESTASIS™.

Clinical Evaluations:

Four multicenter, randomized, controlled clinical studies were performed in approximately 1200 patients with moderate to severe keratoconjunctivitis sicca. RESTASIS demonstrated statistically significant increases in Schirmer wetting versus vehicle at six months in patients whose tear production was presumed to be suppressed due to ocular inflammation. This effect was seen in approximately 15% of treated patients. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

No increase in bacterial or fungal ocular infections was reported following administration of RESTASIS™.

INDICATIONS AND USAGE

RESTASIS™ is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

CONTRAINDICATIONS

RESTASIS™ is contraindicated in patients with active ocular infections and in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

WARNING

RESTASIS™ has not been studied in patients with a history of herpes keratitis.

PRECAUTIONS

General. For ophthalmic use only.

Information for Patients:

The emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Do not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion.

RESTASIS™ should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of RESTASIS.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 1000 and 500 times greater, respectively, than the daily human dose of one drop (28 µL) of 0.05% RESTASIS™ BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Cyclosporine has not been found mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE).

No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 15,000 times the human daily dose of 0.001 mg/kg/day) for 9 weeks (male) and 2 weeks (female) prior to mating.

Pregnancy-Teratogenic effects:

Pregnancy category C.

Teratogenic effects: No evidence of teratogenicity was observed in rats or rabbits receiving oral doses of cyclosporine up to 300 mg/kg/day during organogenesis. These doses in rats and rabbits are approximately 300,000 times greater than the daily human dose of one drop (28 µl) 0.05% RESTASIS™ BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Non-Teratogenic effects: Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution, USP, was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 30,000 and 100,000 times greater, respectively than the daily human dose of one-drop (28 µl) of 0.05% RESTASIS™ BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17/mg/kg/day or 30 mg/kg/day, respectively, during organogenesis.

These doses in rats and rabbits are approximately 17,000 and 30,000 times greater, respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 post partum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 45,000 times greater than the daily human topical dose, 0.001 mg/kg/day, assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (15,000 times greater than the daily human dose).

There are no adequate and well-controlled studies of RESTASIS™ in pregnant women. RESTASIS™ should be administered to a pregnant woman only if clearly needed.

Nursing Mothers:

Cyclosporine is known to be excreted in human milk following systemic administration but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of RESTASIS™, caution should be exercised when RESTASIS™ is administered to a nursing woman.

Pediatric Use:

The safety and efficacy of RESTASIS™ have not been established in pediatric patients below the age of 16.

Geriatric Use:

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

ADVERSE REACTIONS

The most common adverse event following the use of RESTASIS™ was ocular burning (17%).

Other events reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

DOSAGE AND ADMINISTRATION

Invert the unit dose vial a few times to obtain a uniform, white, opaque emulsion before using. Instill one drop of RESTASIS™ twice a day in each eye approximately 12 hours apart. RESTASIS™ can be used concomitantly with artificial tears, allowing a 15 minute interval between products. Discard vial immediately after use.

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HOW SUPPLIED

RESTASIS™ is packaged in single use vials. Each vial contains 0.4 mL fill in a 0.9 mL LDPE vial; 32 vials are packaged in a polypropylene tray with an aluminum peelable lid.

RESTASIS™ 32 Vials 0.4 mL each-NDC 0023-9163-32

Storage: Store RESTASIS™ at 15° to 25° C (59° to 77° F).

KEEP OUT OF THE REACH OF CHILDREN.

Rx Only



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Irvine, CA 92612, U.S.A.

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/s/

Wiley Chambers
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